REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-7, 9-11, 13 and 14 are elected and will be active in this application subsequent to entry of this Amendment. Claim 1 has been amended as shown above and discussed in more detail below.

The Examiner has maintained the restriction requirement and only claims 1-14 have been examined (paragraphs 1-2 of the Office Action). Claim 14 was initially considered a separate invention and has now been accepted as part of Group I. However, the Examiner includes a footnote in this regard suggesting that claim 14 is considered to be inconsistent with the requirements of claim 1. This appears to be because claim 1 is directed to a method for formation of a dispersion, which requires dispersing particles in a polar solvent followed by heating and cooling to improve the specified properties of the particles, while claim 14 requires the additional step of drying the particles. Therefore the Examiner seems to consider that claim 14 does not relate to a method for formation of a dispersion.

Applicants disagree with this view on the basis that drying of the particles, i.e. inclusion of a drying step, need not be the removal of all solvent, but simply provides a solid which is sufficiently "dry" to allow handling. Furthermore, the drying of the particles need not be the final step in the process: the "dry" particles can be re-suspended or hydrated to form a dispersion. This is explained in detail in the second paragraph of page 31 of the description.

Claims 1-14 are rejected as lacking novelty over US 5,670,099 (Morancais *et al.*).

Morancais *et al.* relates to the preparation of submicronic particles in the presence of lipidic vesicles via a dispersion method. Column 10 (lines 20-34) of Morancais *et al.* are considered to disclose a process having all the features of the process of claim 1. This passage refers to the preparation of a lamellar phase by dissolving lipids in a solvent before forming the walls of vesicles, evaporating the solvent, admixing the resulting lipidic combination with an aqueous phase, homogenizing and heating to 10-150 °C (preferably 40-80 °C) for 0.25 hours, followed by cooling to ambient temperature. The homogenization-heating-cooling cycle is repeated at least once. The listed solvents include polar solvents such as alcohols.

Morancais *et al.* specifically refers to formation of a *lamellar* phase, whereas claim 1 of the current application refers to the formation of a dispersion comprising *non-lamellar* amphiphile particles. The current application clearly differentiates between lamellar and non-

lamellar particles, in particular in the section bridging pages 11 and 12 of the application. The term "lamellar particle" is used in the current application to describe vesicular particles characterized in that they comprise one or more outer lamellar bilayers of amphiphile, surrounding an inner solvent compartment (page 12, second paragraph). This is the usual meaning of this term in the art. In contrast, the "non-lamellar particles" of the current application may have a lamellar surface, but have a non-lamellar core region, rather than a solvent core region.

Furthermore, the claimed method requires formation of a dispersion of lamellar (or optionally non-lamellar) particles comprising at least one structuring agent. It appears that either the need for a structuring agent in the current claims has been overlooked, or the term "structuring agent" is being construed so as to include a "lipid capable of forming vesicles".

Finally, and most importantly, the heating-cooling treatment of Morancais *et al.* is part of the process of lamellar phase formation, i.e. it is one stage in the preparation of a dispersion, it is not heat-treatment of a dispersion of particles, as required by the current claim 1.

Example 1 of Morancais *et al.* makes clear that the homogenization-heating-cooling treatment in stage 2 of the process of Morancais *et al.* results in the formation of a lamellar phase, which is subsequently treated by stirring/shaking to obtain a dispersion. It is clear that there is no heat treatment of a dispersion of particles disclosed in Morancais *et al.*

In view of the distinctions outlined above, it is clear that the current claims are novel over Morancais *et al.*

The Examiner has disregarded the requirement that the process results in the formation of particles with improved phase behavior, particle size distribution and/or storage stability. The requirements that the heating is to a suitable temperature for a time sufficient to provide these improvements have also been disregarded. In order to advance examination and ensure that these features are considered claim 1 is above amended to specify the particular reaction conditions used. There is basis in page 13, lines 1-3 and claim 15 of the application to specify that the heating temperature is 80 to 150 °C for a time of 1 minute to 4 hours. With this amendment to claim 1, claims 8 and 12 become redundant and are deleted.

The Examiner asserts the claim in which both non-lamellar and lamellar particles are dispersed to be obvious in view of the disclosures of Morancais *et al.* The Examiner considers

that the same process is disclosed by Morancais *et al.* and this would be expected to form non-lamellar phases at the phase transition temperature, which would be expected to vary based on the amphiphiles, polar solvent etc. which are used. Morancais *et al.* specifies heating conditions of 10-150 °C for 0.25 hours (15 minutes). The preferred heating temperature is 40-80 °C, thus Morancais *et al.* teaches away from the range of temperatures used in amended claim 1 of the current application. Moreover, as noted above the process of Morancais does not involve heat-treatment of a dispersion of particles, as required by the current invention. There is no discussion of this feature or its possible effects in Morancais *et al.*, which therefore cannot provide any motivation for the skilled worker to develop the current process.

In paragraph 16 of the Office Action claims 1-14 are rejected as being obvious over US 6,482,517 (Anderson I) in view of US 2003/0232340 (Anderson II).

The Examiner considers that the reference to Anderson I disclosing "methods for producing dispersions of coated particles of a wide range of liquid crystalline phases... includ[ing] heating-cooling temperature cycles..." in paragraph [0057] of Anderson II would be enough to make the skilled worker perform the process disclosed in Example 10 of Anderson I, in order to achieve the advantages taught in Anderson II.

Applicants point out that in Example 10 of Anderson I the dispersion of microparticles is not formed until *after* the heating and cooling steps; in fact after acidification, stirring, shaking and sonication steps which follow the heating and cooling. The current process requires formation of a dispersion of particles, which are subsequently heated and cooled. It is clear, therefore, that the process disclosed in Anderson I is significantly different from that of the current invention.

Anderson II states that "dispersing cubic and hexagonal phases is... different from dispersing the lamellar phase... sonicating lamellar phase or lamellar phase-forming lipids in water, often does not work with cubic and hexagonal phases... " and "...the present inventor described methods for producing coated particles of a wide range of liquid crystalline phases including cubic and hexagonal. These methods include... heating-cooling temperature cycles... and other methods for solid, typically brittle coating phases, in combination with sonication or other steps for cracking the coated material into coated particles containing liquid crystal.", see paragraph [0057].

The above confirms that the particles produced by the process of Anderson I differ from those of the current invention, and that the processes themselves also differ. Anderson I is directed to forming coated lamellar particles. The current application forms non-lamellar particles. Anderson I forms a dispersion of particles as the final step in its process, by means of stirring, shaking and sonication. The current process requires formation of a dispersion of particles *prior* to heating and cooling treatment.

Furthermore, Anderson II rejects non-lamellar particles (as defined in the current invention), later in paragraph [0057], stating that "...particles of reversed cubic and reversed hexagonal phases with a distinct surface phase comprising a lamellar [or] crystalline lamellar... phase... are not useful *per se* in the instant invention, because they do not allow diffusion of the analyte into the liquid crystal...".

In summary, it is clear that the process of Anderson I is not the same as that of the current invention and would not lead to the same products. Anderson II rejects the particles formed in the process of the current invention in terms of their suitability for the applications of interest in that document. Hence there is no incentive or teaching in Anderson I or Anderson II which could direct the skilled worker to develop the current invention, either alone or in combination. There is no reason for the skilled man to contemplate making non-lamellar particles on the basis of the teaching of these documents, nor do these documents teach the skilled worker how such particles may be obtained.

The examiner is requested to consider the following general comments.

It is important to appreciate that the compositions of the present invention are not fully defined by their components. Just as, for example, an emulsion differs in properties from the same two liquids present in two un-mixed layers, so the presence of the particles in the compositions of the present invention, their sizes, size distributions, and internal structures play a key role in defining the properties of the compositions.

Taking this key issue first, it is noted that the Examiner (incorrectly) argues in paragraph 16 that modifying process conditions such as temperature is not a patentable modification without showing criticality for a result-effective variable. In other words, a difference in the method of the present invention, being the addition of a high temperature step, is not considered to have a technical effect that can be ascribed to this. Such a technical effect is, however,

exhaustively documented in the Examples of the application, and is a key contribution of the present invention.

In the present case, there are two competing issues of thermodynamic and kinetic stability. The thermodynamic form of the individual particles is non-lamellar, but the kinetic barrier is so high that it would take months or years for them to transform into a non-lamellar state under usual storage conditions. Conversely, the non-lamellar particles are generally thermodynamically unstable with respect to conversion into a bulk non-lamellar phase (with a separate solvent phase), corresponding to the separation of an oil-in-water emulsion.

The present inventors have now established that the presence of "contaminant" lamellar particles in the dispersion, and a broad size distribution, tends to cause faster separation of the particles into bulk phases. Unexpectedly, they have found that the heat treatment step described in the present application has the twin effects of bringing essentially all particles into the thermodynamic non-lamellar state, while achieving a non-thermodynamic narrowing of the particle size distribution. The combination of these effects then results in a dispersion which is thermodynamically stable with respect to phase behavior and surprisingly kinetically stable with respect to fusion of the particles and separation into bulk phases.

Consider also Examples 2 and 3 of the present application, in which a dispersion is formed using conventional methods, analysed for phase behavior, heat-treated and then re-analysed. In the first analysis (shown in Figure 3), very few of the particles were seen to be non-lamellar, while following the heat treatment step, essentially all had the structure shown in Figure 4. Example 16 and Figures 14 and 16 then show the resultant effect of this structural change: The untreated peak of b) from Fig 14 becomes bi-modal and shifts to larger diameter as peak a) of Fig 16. In contrast, peak b) of Figure 16 is essentially indistinguishable from the corresponding peak (c) of Figure 14. It is thus clear that both the individual particles, and the dispersion as a whole are significantly affected by the heat treatment step.

As further explanation and background to the invention, submitted herewith a paper published by the present inventors with regard to the method of the invention (Langmuir **2005**, 2569-2577). This is referred to herein as Barauskas *et al.*. It must be seen as evident that a method having no technical effect is unlikely to merit a full paper in such a major international journal, and thus counsel submits that the present method is clearly recognized as making a

significant contribution to the relevant art. The issues of stability, particle sizes and phase behavior are also discussed in some detail in this paper.

In view of the above discussion, and in particular in view of Figure 3, which shows directly that particles formed by conventional methods are largely lamellar, it is clear that there is no evidence to suggest any great proportion of these particles of in fact inhabit their thermodynamic state. Certainly, Figure 3 suggests than much less than 50%, and evidently less than 75% do so. Figure 5 of the enclosed document Barauskas *et al.* provides further evidence of this.

Considering non-obviousness, the examiner's dismissal of any technical difference provided by temperature changes serves most clearly to demonstrate that the effects observed by the present inventors were highly unexpected. There is no prior art suggesting that phase behavior, particle size distribution, or particle distribution stability could be affected by heat treatment, and certainly nothing to suggest the positive contribution to all of these factors demonstrated in the Examples and Figures. Again a nine-page paper in a major international journal is never allocated to processes having no value. There is clearly, therefore, a significant technical contribution made to the art by the methods of the present invention, and there is absolutely no suggestion in the prior art that this could be the case. This contribution is demonstrated in the Examples of the application and further in the experiments described in Barauskas *et al.*.

The problem of the present invention is to provide and improve the properties of non-lamellar dispersions. This is achieved, as clearly shown in the Examples of the application and in Barauskas *et al.*, by the heat treatment method claimed. No prior art suggests this method or its benefits, and thus it cannot be seen as obvious. The independent claims of the amended claim set thus all embody an inventive step.

Counsel is in the process of securing a supplemental declaration under Rule 63 from the inventors providing full dates for the filing of the three GB applications. The basic information is already of record in the international application papers, such as page 1 of the application published as WO 2005/014162.

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith

(or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 14-1140.

Respectfully submitted,

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